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TITLE: Peptide inhibitors of mitogenesis and motogenesis

BSPR:
p66.sup.Shc is encoded by an alterantively spliced transcript (Migliaccio et al, in preparation). Experimental evidence indicates that Shc proteins are implicated in the transduction of signals generated by tyrosine kinase receptors. Among these, Shc proteins are rapidly tyrosine-phosphorilated in response to activation of the EGF (Pelicci et al, ibid) and PDGF (unpublished data) receptors, Erb-B-2 (Segatto et al., Oncogene 2105-2112 (1993)), Src and Fps (McGlade et al, Proc. Natl. Acad. Sci. U.S.A. 89: 8869-8873 (1992)). Overexpression of Shc proteins induces neurite outgrowth in PC12 pheochromocytoma cells, and this effect is blocked by the expression of a dominant-negative Ras mutant (Rozakis-Adcock et al., Nature 360: 689-692 (1992)). Upon cell stimulation by certain growth factors, Shc proteins form stable complexes with the Grb2/Sem5 adaptor (Lowenstein et al., Cell 70: 431-442 (1992); Rozakis-Adcock et al., ibid). The latter adaptor is known to activate Ras functions by recruiting SoS, a guanine nucleotide exchanger factor (Li et al., Nature 363: 85-87 (1993); Gale et al., Nature 363: 88-92 (1993); Rozakis-Adcock et al., Nature 363: 83-85 (1993); Egan et al., Nature 363: 45-51 (1993); Simon et al., Cell 73: 169-177 (1993); Oliver et al., Cell 73: 179-191 (1993)) to the membrane.

DEPR:
By phosphopeptide mapping and mutation analysis it has been shown that the major phosphorylation site of Shc in EGF-treated cells is Y.sup.317 (Salcini et al., in preparation). To ascertain that the same residue is also phosphorylated after SF/HGF treatment, a tagged SHC cDNA with a Y.sup.317 .fwdarw.F mutation was expressed into A549 cells. In these cells, after SF/HGF treatment, the Y.sup.317 .fwdarw.F mutant, selectively immunoprecipitated by anti- "tag" antibodies was not phosphorylated on tyrosine (FIG. 1D).

DEPR:
In conclusion, a peptide having a length of e.g. 4 to 20 amino acids encompassing the docking site of Shc (Y.sup.317 VNV) (SEQ. ID NO: 3), particularly the peptide H-Asp-Asp-Pro-Ser-Tyr*-Val-Asn-Val-Gln-OH (SEQ. ID NO: 27),(DDPSY*VNVQ) and a peptide having a length of e.g. 4 to 20 amino acids encompassing the Tyr.sup.1356 recognition motif of the hepatocyte growth factor receptor (Y.sup.1356 VNV) (SEQ. ID NO: 3), particularly the peptide H-Val-Asn-Ala-Thr-Tyr*-Val-Asn-Val-Lys-OH (SEQ. ID NO: 28) (VNATY*VNVK), wherein Tyr* (Y*) represents a phosphorylated or unphosphorylated tyrosine residue, are able to bind Grb2 -SH2 domain. Thus, they are useful to compete for and to prevent association of the SH2 of Grb2 protein with tyrosine phosphorylated receptors such as activated hepatocyte growth factor receptor (HGF/SF receptor), PDGF receptor, EGF receptor or with other cytosolic tyrosine phosphorylated transducers such as Shc or IRS-1 protein, preventing mitogenesis and hence tumoral proliferation.

DEPR:
On the other hand, peptides encompassing the Tyr.sup.1356 or the Tyr.sup.1349 recognition motif of the hepatocyte growth factor receptor (Y.sup.1356 VNV or Y.sup.1349 VHV respectively) (SEQ. ID NOS:3and 4), particularly the above mentioned peptide H-Val-Asn-Thr-Tyr*-Val-Asn Val-Lys-OH (SEQ. ID NO: 28) (VNATY*VNVK) and the peptide H-Ile-Gly-Glu-His-Tyr*-Val-His-Val-Asn-OH (SEQ. ID NO: 30), (IGEHY*VHVN) or a peptide containing both the above mentioned tyrosine residues such as
H-Ile-Gly-Glu-His-Tyr*-Val-His-Val-Asn-Ala-Thr-Tyr*-Val-Asn-Val-Lys-OH (SEQ. ID NO: 31), (IGEHY*VHVNATY*VNVK) wherein Tyr* (Y*) represents phosphorylated or

NO: 31), (IGEHY*VH[redacted]Y*V[redacted]) wherein Tyr* (Y*) represe[redacted]sphorylated or unphosphorylated tyrosine residue, are able to bind Shc-[redacted]2 domain. Thus, they are useful to compete for and to prevent the SH2 association of Shc protein with tyrosine phosphorylated receptors such as activated hepatocyte growth factor receptor, EGF receptors or with other cytosolic tyrosine phosphorylated transducers like IRS-1 or cytosolic tyrosine kinases such as Src, preventing mitogenesis and particularly motogenesis and hence preventing spreading of tumour cells. Thus, the peptides exert antitumoral and antimetastatic actions.